Biological Therapies: Using the Immune System To Treat Cancer

Biological therapy (sometimes called immunotherapy, biotherapy, or biological response modifier therapy) is a relatively new addition to the family of cancer treatments that also includes surgery, chemotherapy, and radiation therapy. Biological therapies use the body's immune system, either directly or indirectly, to fight cancer or to lessen the side effects that may be caused by some cancer treatments.

The immune system is a complex network of cells and organs that work together to defend the body against attacks by "foreign," or "non-self," invaders. This network is one of the body's main defenses against disease. It works against disease, including cancer, in a variety of ways. For example, the immune system may recognize the difference between healthy cells and cancer cells in the body and work to eliminate those that become cancerous.

Cancer may develop when the immune system breaks down or is not functioning adequately. Biological therapies are designed to repair, stimulate, or enhance the immune system's responses.

Immune system cells include the following:

- **Lymphocytes** are a type of white blood cell found in the blood and many other parts of the body. Types of lymphocytes include B cells, T cells, and Natural Killer cells.

B cells (B lymphocytes) mature into plasma cells that secrete antibodies (immunoglobulins), the proteins that recognize and attach to foreign substances known as antigens. Each type of B cell makes one specific antibody, which recognizes one specific antigen.

T cells (T lymphocytes) directly attack infected, foreign, or cancerous cells. T cells also regulate the immune response by signaling other immune system defenders. T cells work primarily by producing proteins called lymphokines.

Natural Killer cells (NK cells) produce powerful chemical substances that bind to and kill any foreign invader. They attack without first having to recognize a specific antigen.

- **Monocytes** are white blood cells that can swallow and digest microscopic organisms and particles in a process known as phagocytosis. Monocytes can also travel into tissue and become **macrophages**, or "big eaters."

Cells in the immune system secrete two types of proteins: antibodies and cytokines. Antibodies respond to antigens by latching on to, or binding with, the antigens. Specific antibodies match specific antigens, fitting together much the way a key fits a lock. Cytokines are substances produced by some immune system cells to communicate with other cells. Types of cytokines include lymphokines, interferons, interleukins, and colony-stimulating factors.

Biological Response Modifiers

Some antibodies, cytokines, and other immune system substances can be produced in the laboratory for use in cancer treatment. These substances are often called biological response modifiers (BRMs). They alter the interaction between the body's immune defenses and cancer cells to boost, direct, or restore the body's ability to fight the disease. BRMs include interferons, interleukins, colony-stimulating factors, monoclonal antibodies, and vaccines.

Researchers continue to discover new BRMs, learn more about how they function, and develop ways to use them in cancer therapy. Biological therapies may be used to:

- Stop, control, or suppress processes that permit cancer growth;
- Make cancer cells more recognizable, and therefore more susceptible, to destruction by the immune system;
- Boost the killing power of immune system cells, such as T cells, NK cells, and macrophages;
- Alter cancer cells' growth patterns to promote behavior like that of healthy cells;
- Block or reverse the process that changes a normal cell or a precancerous cell into a cancerous cell;
- Enhance the body's ability to repair or replace normal cells damaged or destroyed by other forms of cancer treatment, such as chemotherapy or radiation; and
- Prevent cancer cells from spreading to other parts of the body.

Some BRMs are a standard part of treatment for certain types of cancer, while others are being studied in clinical trials (research studies with patients). BRMs are being used alone or in combination with each other. They are also being used with other treatments, such as radiation therapy and chemotherapy.

Interferons (IFN)

Interferons are types of cytokines that occur naturally in the body. They were the first cytokines produced in the laboratory for use as BRMs. There are three major types of interferons—interferon alpha, interferon beta, and interferon gamma; interferon alpha is the type most widely used in cancer treatment.

Researchers have found that interferons can improve the way a cancer patient's immune system acts against cancer cells. In addition, interferons may act directly on cancer cells by slowing their growth or promoting their development into cells with more normal behavior.

Researchers believe that some interferons may also stimulate NK cells, T cells, and macrophages, boosting the immune system's anticancer function.

The U.S. Food and Drug Administration (FDA) has approved the use of interferon alpha for the treatment of certain types of cancer, including hairy cell leukemia, melanoma, chronic myeloid leukemia, and AIDS-related Kaposi's sarcoma. Studies have shown that interferon alpha may also be effective in treating other cancers such as metastatic kidney cancer and non-Hodgkin's lymphoma. Researchers are exploring combinations of interferon alpha and other BRMs or chemotherapy in clinical trials to treat a number of cancers.

Interleukins (IL)

Like interferons, interleukins are cytokines that occur naturally in the body and can be made in the laboratory. Many interleukins have been identified; interleukin-2 (IL-2 or aldesleukin) has been the most widely studied in cancer treatment. IL-2 stimulates the growth and activity of many immune cells, such as lymphocytes, that can destroy cancer cells. The FDA has approved IL-2 for the treatment of metastatic kidney cancer and metastatic melanoma.

Researchers continue to study the benefits of interleukins to treat a number of other cancers, including colorectal, ovarian, lung, brain, breast, prostate, some leukemias, and some lymphomas.

Colony-Stimulating Factors (CSFs)

Colony-stimulating factors (CSFs) (sometimes called hematopoietic growth factors) usually do not directly affect tumor cells; rather, they encourage bone marrow cells to

divide and develop into white blood cells, platelets, and red blood cells. Bone marrow is critical to the body's immune system because it is the source of all blood cells.

The CSFs' stimulation of the immune system may benefit patients undergoing cancer treatment. Because anticancer drugs can damage the body's ability to make white blood cells, red blood cells, and platelets, patients receiving anticancer drugs have an increased risk of developing infections, becoming anemic, and bleeding more easily. By using CSFs to stimulate blood cell production, doctors can increase the doses of anticancer drugs without increasing the risk of infection or the need for transfusion with blood products. As a result, researchers have found CSFs particularly useful when combined with high-dose chemotherapy.

Some examples of CSFs and their use in cancer therapy are as follows:

- **G-CSF (filgrastim)** and **GM-CSF (sargramostim)** can increase the number of white blood cells, thereby reducing the risk of infection in patients receiving chemotherapy. G-CSF and GM-CSF can also stimulate the production of stem cells in preparation for stem cell or bone marrow transplants;

- **Erythropoietin** can increase the number of red blood cells and reduce the need for transfusions in patients receiving chemotherapy; and

- **Oprelvekin** can reduce the need for platelet transfusions in patients receiving chemotherapy.

Researchers are studying CSFs in clinical trials to treat some types of leukemia, metastatic colorectal cancer, melanoma, lung cancer, and other types of cancer.

Monoclonal Antibodies (MOABs)

Researchers are evaluating the effectiveness of certain antibodies made in the laboratory called monoclonal antibodies (MOABs or MoABs). These antibodies are produced by a single type of cell and are specific for a particular antigen. Researchers are examining ways to create MOABs specific to the antigens found on the surface of the cancer cell being treated.

MOABs are made by injecting human cancer cells into mice so that their immune systems will make antibodies against these cancer cells. The mouse cells producing the antibodies are then removed and fused with laboratory-grown cells to create "hybrid" cells called hybridomas. Hybridomas can indefinitely produce large quantities of these pure antibodies, or MOABs.

MOABs may be used in cancer treatment in a number of ways:

- MOABs that react with specific types of cancer may enhance a patient's immune response to the cancer.
- MOABs can be programmed to act against cell growth factors, thus interfering with the growth of cancer cells.
- MOABs may be linked to anticancer drugs, radioisotopes (radioactive substances), other BRMs, or other toxins. When the antibodies latch onto cancer cells, they deliver these poisons directly to the tumor, helping to destroy it.
- MOABs may help destroy cancer cells in bone marrow that has been removed from a patient in preparation for a bone marrow transplant.

MOABs carrying radioisotopes may also prove useful in diagnosing certain cancers, such as colorectal, ovarian, and prostate.

Rituxan® (rituximab) and Herceptin® (trastuzumab) are two monoclonal antibodies approved by the FDA. Rituxan is used for the treatment of B-cell non-Hodgkin’s lymphoma that has returned after a period of improvement or has not responded to chemotherapy. Herceptin is used to treat metastatic breast cancer in patients with tumors that produce excess amounts of a protein called HER-2. (Approximately 30 percent of breast cancer tumors produce excess amounts of HER-2.) Researchers are testing MOABs in clinical trials to treat lymphomas, leukemias, colorectal cancer, lung cancer, brain tumors, prostate cancer, and other types of cancer.

Cancer Vaccines

Cancer vaccines are another form of biological therapy currently under study. Vaccines for infectious diseases, such as measles, mumps, and tetanus, are effective because they expose the immune system to weakened versions of the disease. This exposure causes the immune system to respond by producing antibodies. Once the immune system has created antibodies, some of the activated immune cells remember the exposure. Therefore, the next time the same antigen enters the body, the immune system can respond more readily to destroy it.

For cancer treatment, researchers are developing vaccines that may encourage the immune system to recognize cancer cells. These vaccines may help the body reject tumors and prevent cancer from recurring. In contrast to vaccines against infectious diseases, cancer vaccines are designed to be injected *after* the disease is diagnosed, rather than *before* it develops. Researchers are also investigating ways that cancer vaccines can be used in combination with other BRMs. Cancer vaccines are being studied in the treatment of many types of cancer, including melanoma, lymphomas, and cancers of the kidney, breast, ovaries, prostate, colon, and rectum.

Side Effects

Like other forms of cancer treatment, biological therapies can cause a number of side effects, which can vary widely from patient to patient. Rashes or swelling may develop at the site where the BRMs are injected. Several BRMs, including interferons and interleukins, may cause flu-like symptoms including fever, chills, nausea, vomiting, and appetite loss. Fatigue is another common side effect of BRMs. Blood pressure may also be affected. The side effects of IL-2 can often be severe, depending on the dosage given. Patients need to be closely monitored

during treatment. Side effects of CSFs may include bone pain, fatigue, fever, and appetite loss. The side effects of MOABs vary, and serious allergic reactions may occur. Cancer vaccines can cause muscle aches and fever.

Clinical Trials

Information about ongoing clinical trials involving these and other biological therapies is available from the Cancer Information Service (see below) or from the National Cancer Institute's cancerTrials™ Web site at http://cancertrials.nci.nih.gov on the Internet.

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Sources of National Cancer Institute Information

Cancer Information Service
Toll-free: 1–800–4–CANCER (1–800–422–6237)
TTY (for deaf and hard of hearing callers): 1–800–332–8615

NCI Online
Internet
Use http://www.cancer.gov to reach NCI's Web site.

CancerMail Service
To obtain a contents list, send e-mail to cancermail@icicc.nci.nih.gov with the word "help" in the body of the message.

CancerFax® fax on demand service
Dial 301–402–5874 and listen to recorded instructions.

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